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MARTIN A. HAY

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Signature Date 7/3/06

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	McGLYNN, Paul
	:	BAKALE, Roger
	:	STURGE, Craig
Serial No.	:	10/728,873
Filing Date	:	December 8, 2003
For	:	LEVALBUTEROL SALT
Art Unit	:	1621
Examiner	:	PUTTLITZ, Karl J.
Confirm No.	:	1167
Docket No.	:	00324/US1
Customer No.	:	024330

DECLARATION UNDER 37 C.F.R. 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
UNITED STATES

Sir:

We, Paul McGlynn, Roger Bakale and Craig Sturge, declare that:

We are the inventors and applicants in this application.

Prior to October 10, 2002, we had completed our invention in the United States as evidenced by the following:

Prior to October 10, 2002, micronized crystals of levalbuterol L-tartrate had been prepared and tested in a metered dose inhaler, as described in the attached copies of two e-mail messages with attachments sent by one of us, Paul McGlynn, to Douglas Reedich and James Kellerman in the patent department of Sepracor Inc on March 4, 2002 and March 6, 2002 respectively.

We further declare that all statements made herein of our own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of the application or any patent issuing thereon.

_____ _____

McGLYNN, Paul Date

_____ _____

BAKALE, Roger Date

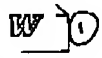
_____ _____

STURGE, Craig Date

James Kellerman

From: Paul McGlynn
Sent: Monday, March 04, 2002 3:13 AM
To: Doug Reedich; James Kellerman
Cc: James Conners; Adam Sabouni; Leigh Ellen Baca; Craig Sturge

Doug,
Here at last is the lev patent info. I'm sorry it hasn't come earlier but I've been out of the office for most of the year so far and I had to get my group and some outside contractors to fill in some of the pieces. I will send what I have to you over the next day or so as I'm on vacation and there are some pretty large files to download with pictures. Here is the first update


Patent process description1.do...


0410005-SEMs.doc

outlining the chemistry.

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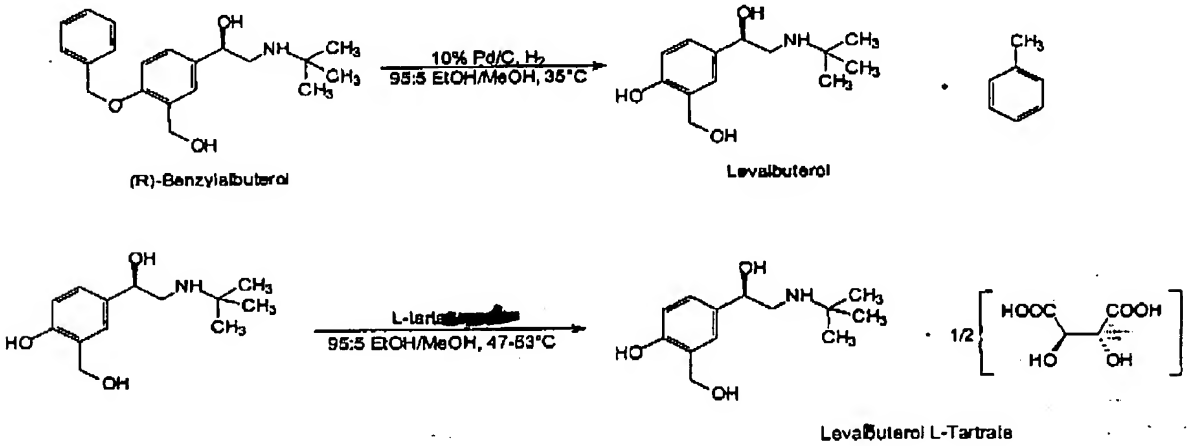
(1)

Production of Levalbuterol Tartrate

Levalbuterol L-tartrate (LevTA) is prepared from (*R*)-benzylalbuterol (an intermediate in the synthesis of levalbuterol hydrochloride) by catalytic hydrogenation to form levalbuterol free base *in situ*, followed by addition of ethanolic L-tartaric acid to form the hemitartrate salt. A reaction schematic for the synthesis is given in Figure 1.

Figure 1. Reaction Scheme for the Synthesis of Levalbuterol L-tartrate

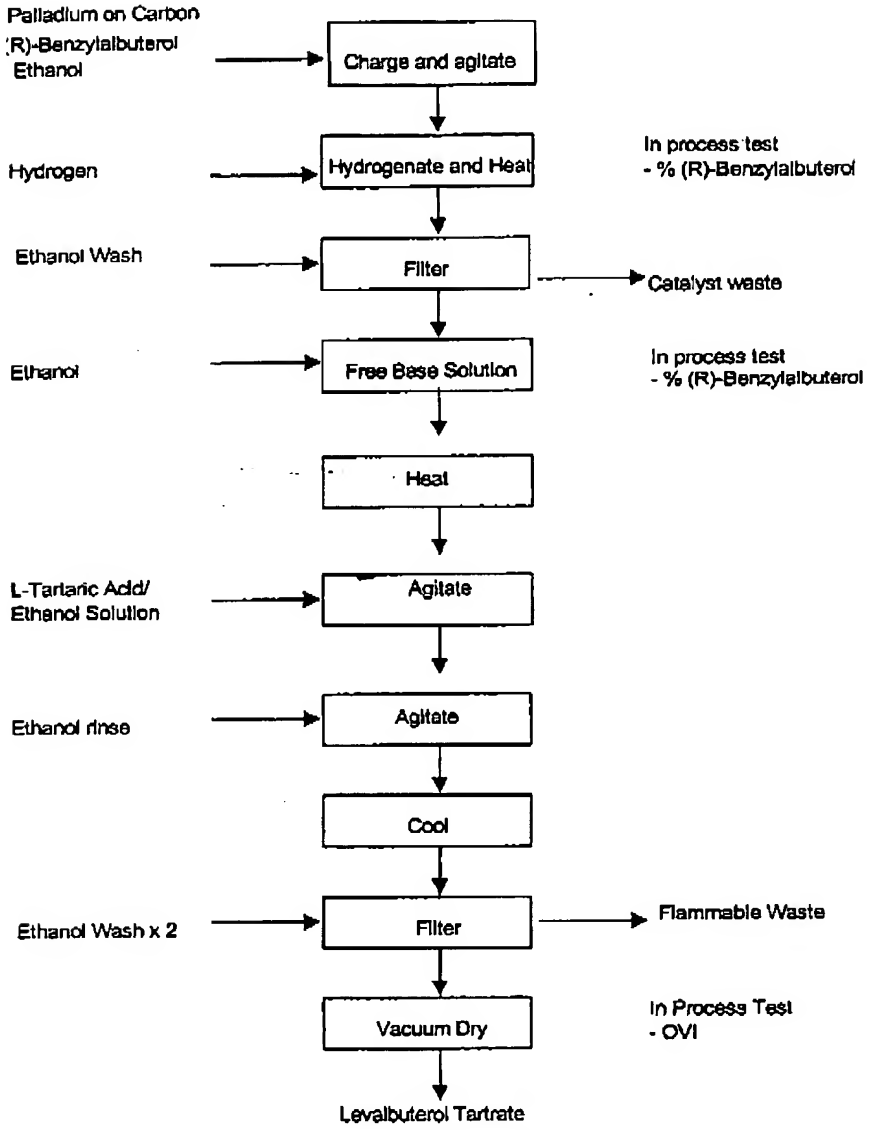


PROCESS DESCRIPTION

(*R*)-Benzylalbuterol (54.6 mol), 10% palladium on carbon (50% water wet, 0.03 mol Pd), and ethanol (denatured with 5% methanol) are charged to a suitable pressure reactor and hydrogen is introduced at 50 psig. The mixture is heated to 33-37 °C with agitation until the level of (*R*)-benzylalbuterol is less than 0.20%, as determined by HPLC. The mixture is filtered to remove the catalyst. The filtrate is transferred to a suitable glass lined reactor and ethanol is added to give an approximately 11 wt% solution of levalbuterol free base. In a separate vessel, L-tartaric acid (27.3 mol) is dissolved in ethanol with agitation at approximately 20-25 °C. The free base solution is heated to 47-53 °C and the tartaric acid solution is charged over approximately 120 minutes producing a slurry of the hemitartrate salt. The transfer lines are rinsed with ethanol and then added to the slurry. This mixture is held at approximately 50 °C for 1 hour and then cooled to 19-25 °C linearly over approximately 2 hours. The mixture is filtered and the filter cake is washed with ethanol and then dried in a vacuum tray dryer under vacuum at approximately 40 °C.

A process flow diagram is given in Figure 2 and a detailed description of a representative batch is given in Appendix I.

Figure 2. Process Flow Diagram for Levalbuterol L-Tartrate



The hydrogenation conditions and reaction monitoring are designed to allow complete (<0.1%) debenzylation of (*R*)-benzylalbuterol without over reduction of other functional groups. Failure to adequately control the stoichiometry of the catalyst, temperature range, or reaction times can result in incomplete debenzylation or significant reduction of

other functional groups to create synthetic impurities. Futhermore, the crystallization process does not afford significant purification of the product. Therefore it is essential to adequately control the reaction parameters to minimize the process impurities.

Similarly, the crystallization parameters such as agitation rate, temperature, and tartaric acid addition rate have been designed to provide needles of approximate dimension 10-50 microns in length and 0.2 – 4 microns in width. SEM micrographs are supplied in additional file (0410005-SEMs.wpd).

Crystallization from EtOH/Water, IPA, IPA/Water and ACN all produced crystals of different dimensions from that described above or without striations/fault planes. In each case micronization yielded material which was respirable i.e. NLT 80% < 5 microns but this material re-aggregated upon storage at normal room temperature and humidity conditions.

The optimum crystallization parameters yielded material with OVI ethanol content upon drying of approximately 0.5%.

Failure to adequately control these parameters has been shown to yield material with lower ethanol content (approximately 0.3%) that does not have a stable particle size distribution after micronization. Materials with higher ethanol contents than 0.5% have not yet been examined.

APPENDIX I. DESCRIPTION OF THE PRODUCTION OF LEVALBUTEROL TARTRATE

Representative Pilot Plant Procedure (Batch 041 0014):

1. To reactor R-250 was charged 4.11 kg of L-tartaric acid.
2. To reactor R-250 was charged 21.9 kg of ethanol.
3. The contents of R-250 were agitated at 20-25 °C to form a clear solution and held for later use.
4. Reactor R-311 was charged with 60 g of 10% palladium on carbon.
5. Reactor R-311 was charged with 18.0 kg of (*R*)-benzylalbuterol.
6. The atmosphere of R-311 was evacuated and replaced with nitrogen three times to exclude air.
7. Under vacuum, R-311 was charged with 48.1 kg of ethanol with agitation.
8. The contents of R-311 were evacuated and replaced with nitrogen three times to exclude air.
9. The contents of R-311 were pressurized to 50 psi with nitrogen and then vented.
10. The contents of R-311 were pressurized once with 50 psi of hydrogen, vented, and then repressurized to 50 psi with hydrogen.
11. The temperature was adjusted to 33 to 37 °C.
12. The mixture was agitated at 33 to 37 °C and samples removed at approximately 1 hour intervals for reaction monitoring until the reaction was complete. [Result: after 4.5 hours (*R*)-benzylalbuterol = 0.09%]
13. The hydrogen was vented from reactor R-311 and pressurized with nitrogen to 50 psi 3 times.
14. The contents of R-311 were cooled to 19-25 °C.
15. The contents of R-311 were filtered through a 3 μm and 0.3 μm in-line cartridge filter to reactor R-321.
16. With agitation, R-311 was charged with 25.5 kg of ethanol and filtered through a 3 μm and 0.3 μm in-line cartridge filter to waste drums and a sample removed for density and quantitation of levalbuterol [result: density = 0.787 g/ml and levalbuterol = 0.787 mg/ml].

17. With agitation, R-321 was charged with 59.3 kg of ethanol.

18. The contents of R-321 were heated to 47-53 °C.

19. The tartaric acid solution in R-250 was filtered through a 3 μm polishing filter and charged to R-321 over 120 minutes forming a precipitate.

20. R-250 was rinsed with 6.17 kg of ethanol and charged to R-321.

21. The slurry in R-321 was agitated at 47-53 °C for 63 minutes.

22. The slurry was then cooled to 19-25 °C over 128 minutes.

23. Approximately one-third of the slurry was filtered using centrifuge CE-103.

24. The product was washed with 13.2 kg of ethanol.

25. The product was washed with 12.5 kg of ethanol.

26. The wet product (9.99 kg) was discharged from the centrifuge.

27. Approximately one-half of the remaining slurry was filtered using centrifuge CE-103.

28. The product was washed with 13.4 kg of ethanol.

29. The product was washed with 12.4 kg of ethanol.

30. The wet product (10.29 kg) was discharged from the centrifuge.

31. The remaining portion of the slurry was filtered in centrifuge CE-103.

32. The product was washed with 12.8 kg of ethanol.

33. The product was washed with 12.6 kg of ethanol.

34. The wet product (9.86 kg) was discharged from the centrifuge.

35. The combined wet product was loaded into dryer D-404 and dried at 35-40 °C for 21 hours until the %ethanol was less than 0.5% [Result: %ethanol = 0.49%].

36. The product (16.51 kg) was discharged.

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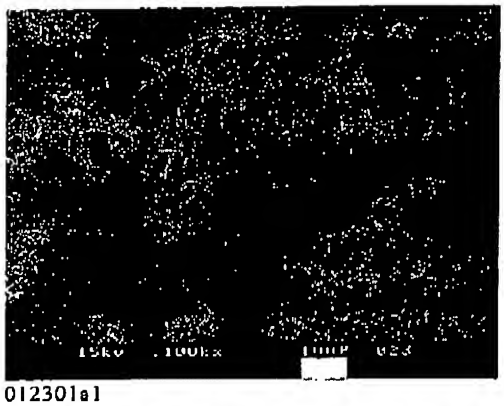
SEM Pictures: **Sample of lot 041-0005 sonicated in hexane (sample prepared 01/23/01)**
GMP 10-kg scale-up batch, Ethanol, 50 °C, TA to FB



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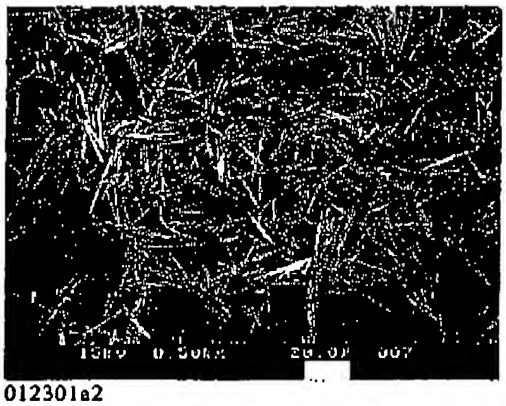

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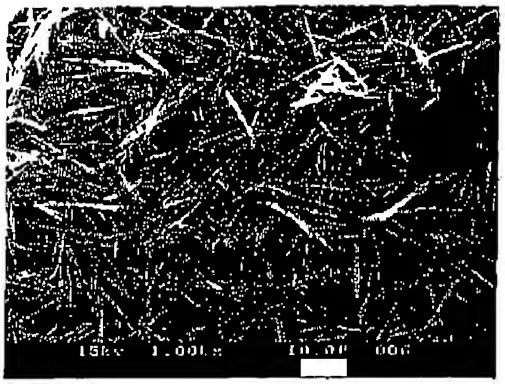

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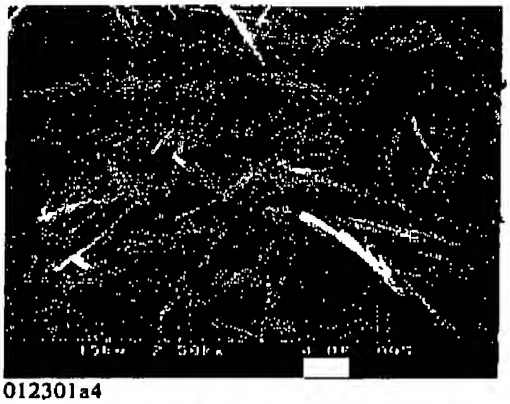

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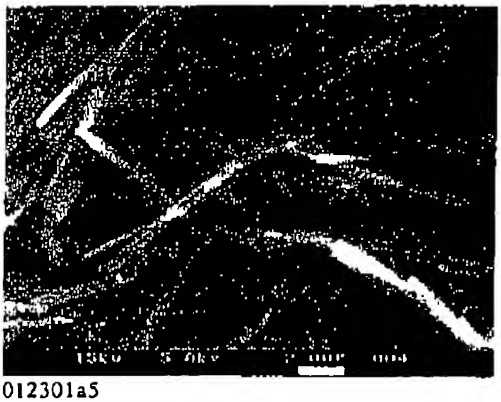

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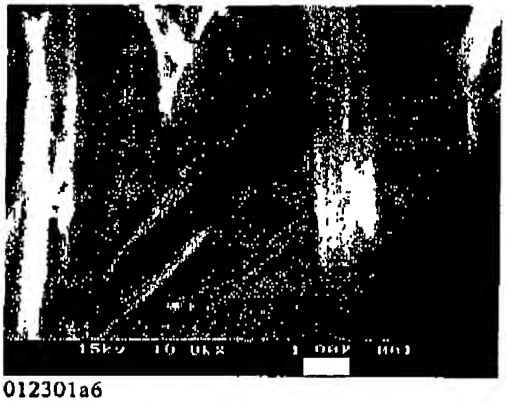

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James Kellerman

From: Paul McGlynn
Sent: Wednesday, March 06, 2002 5:19 PM
To: Doug Reedich; James Kellerman
Cc: Adam Sabouni; Craig Sturge; James Conners; Leigh Ellen Baca
Subject: Lev Patent update

Doug
Please find attached a description of the micronization process(Leigh Ellen) and micronized particles (Cirrus)

W 2 Micronized .evalbuterol Tartra..nsiderations for Lev

W 4 Patent

W 5 SEM summary.doc

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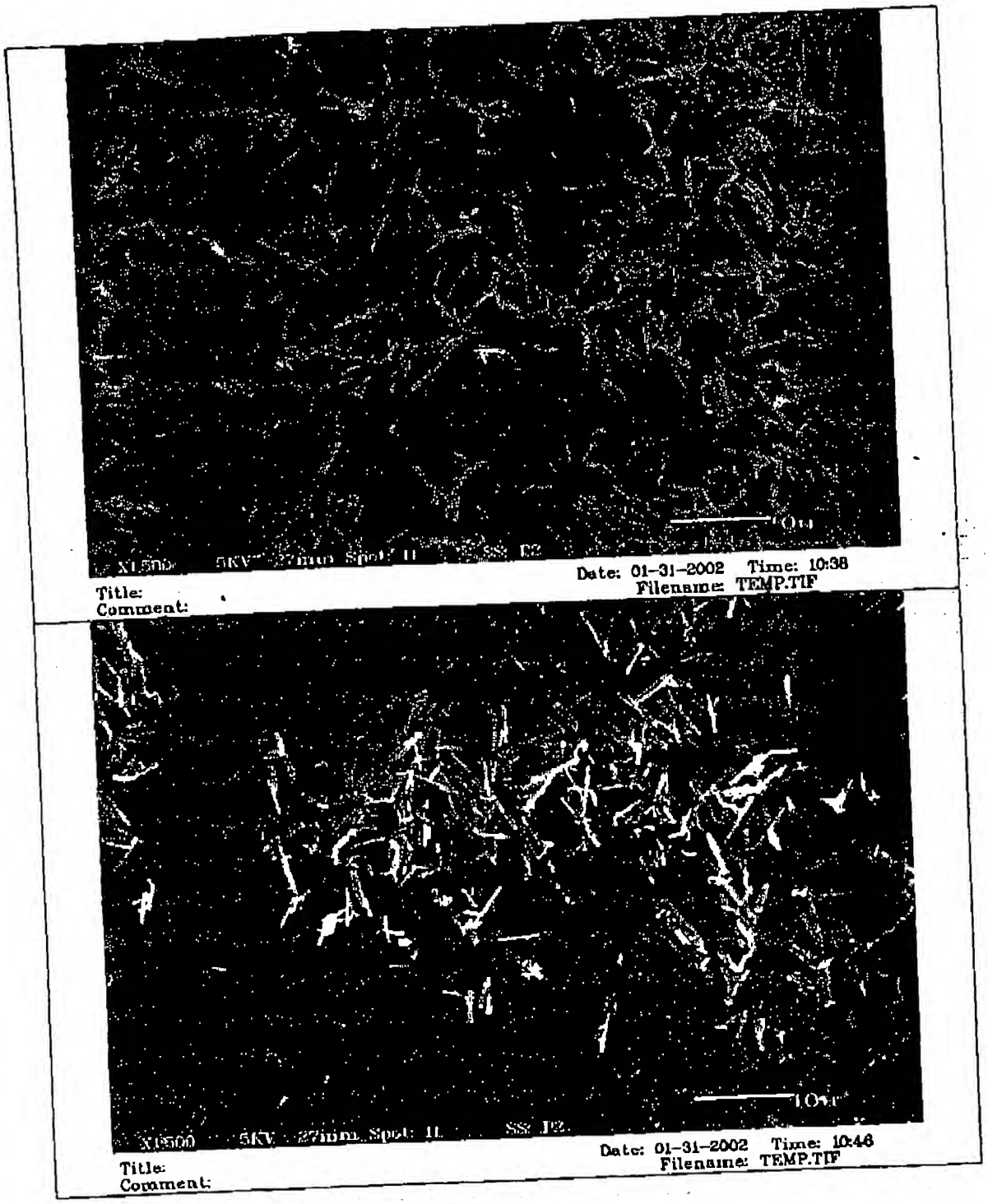

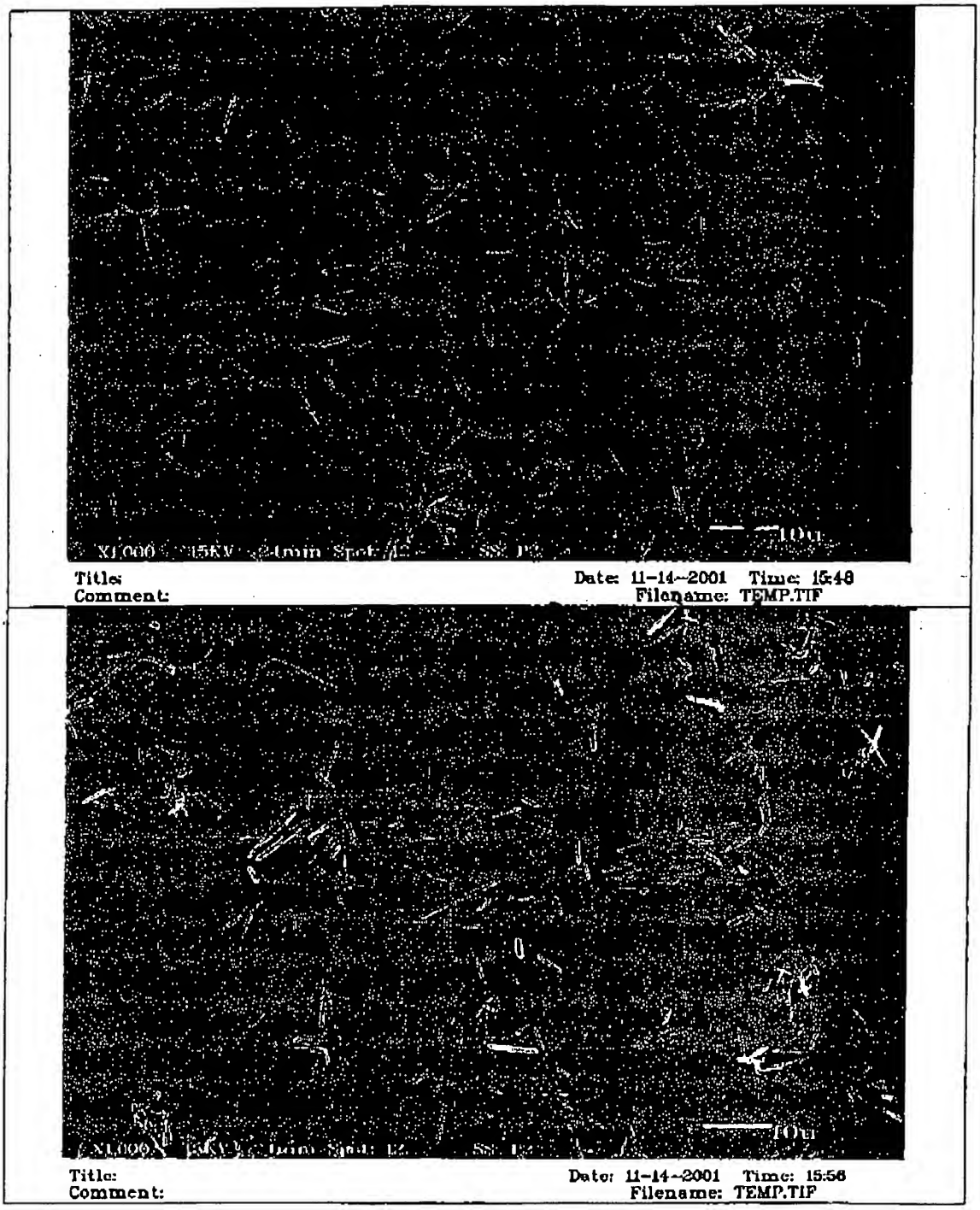

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Patent Considerations for Levalbuterol Tartrate Micronisation Process
Leigh Ellen Baca, Aerosol Development, Sepracor Inc.

Levalbuterol tartrate requires particle size reduction for formulation in a pressurized metered dose inhaler. The ideal method of particle size reduction for levalbuterol tartrate is air-jet micronisation using dry filtered processing air (dewpoint of –40°C).[1] Currently, micronisation of levalbuterol tartrate is achieved using a 4-inch pancake-style fluid energy mill with a venturi pressure of 50 psi and a mill pressure of 100 psi. The mill operator uses a vibratory feeder to supply the unmicronised levalbuterol tartrate to the mill at a rate of 1.4 ± 0.4 kilograms per hour.[2] Levalbuterol tartrate is not a free-flowing powder and must be de-lumped by manually screening the material prior to introducing the unmicronised drug into the hopper.

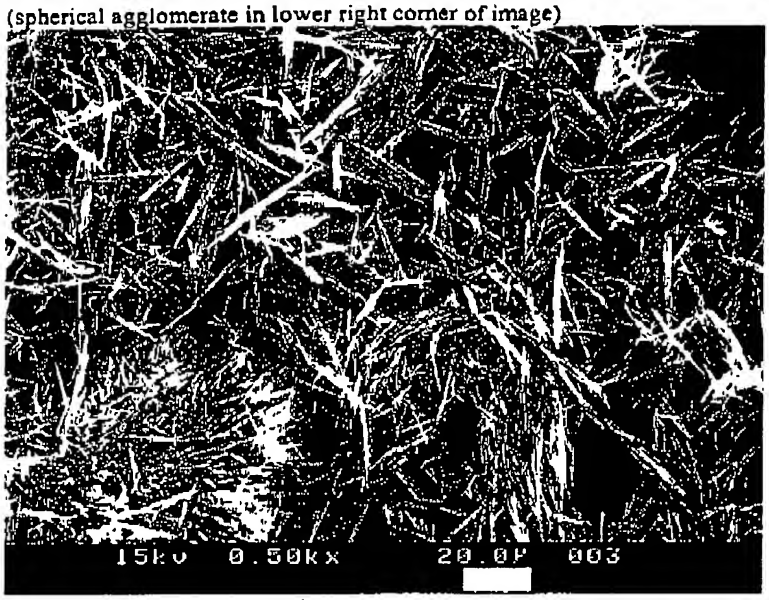
Levalbuterol tartrate feed material is composed of crystalline needles with an aspect ratio of approximately 20:1. The majority of these needles range in length between 15 and 40 micrometers, and may be associated on their long axes. Unmicronised levalbuterol tartrate often contains spherical agglomerates that are approximately 100 micrometers diameter, or fragments thereof (agglomerates may be disrupted with the agitation during manufacture).[3]

The micronisation process also results in crystalline needles. The product material is a mixture of smaller needles (lengths of 0.5 to 3 micrometers) with aspect ratios between 3:1 and 10:1, longer needles (lengths of 3 to 9 micrometers) with aspect ratios of approximately 15:1, and fine particle fragments of approximately 0.5 micrometers. This needle-like product is atypical of micronised materials, which generally are more uniformly spherical in character after processing. Micronised levalbuterol tartrate carries a static charge and may associate in 'static balls' that can be dispersed by sonication. The micronised product is sensitive to high relative humidities and must be protected from the environment by immediately packaging in foil with an argon headspace. Micronisation experiments with sub-optimal feed and pressure conditions have also generated product with similar needle characteristics, though overall particle sizes were slightly increased.

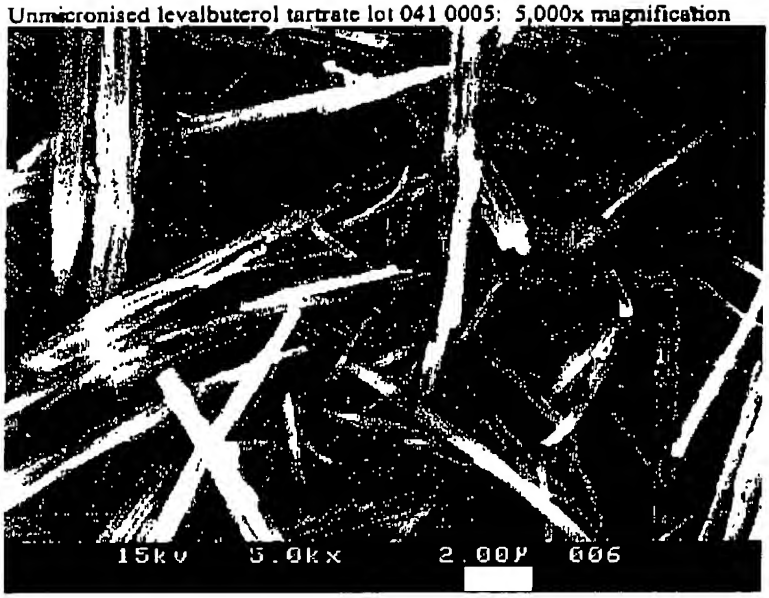
[1] Processing under inert conditions may be a future consideration for this product. This would be accomplished by processing with nitrogen as the micronising gas.
[2] Micronisation of levalbuterol tartrate can also be completed using fluid energy mills of other sizes, but milling pressures and feed rates must be optimized for each size mill.
[3] Refer to scanning electron micrographs of levalbuterol tartrate

Scanning Electron Micrographs : Unmicronised Levalbuterol Tartrate

Unmicronised levalbuterol tartrate lot 041 0005: 500x magnification
(spherical agglomerate in lower right corner of image)

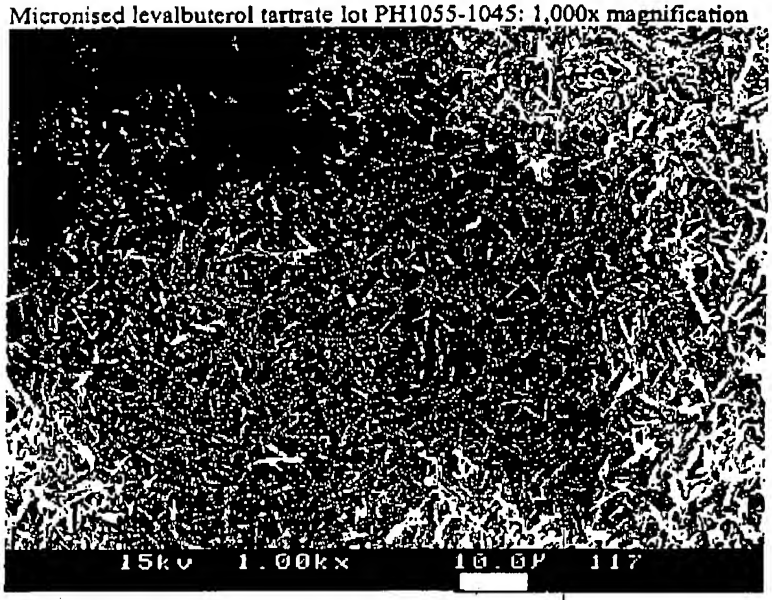


Unmicronised levalbuterol tartrate lot 041 0005: 5,000x magnification

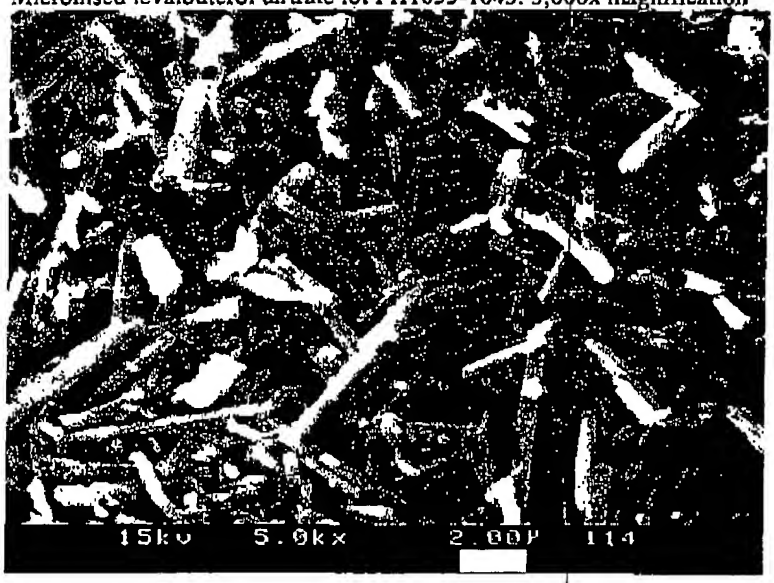


Scanning Electron Micrographs: Micronised Levalbuterol Tartrate

Micronised levalbuterol tartrate lot PH1055-1045: 1,000x magnification



Micronised levalbuterol tartrate lot PH1055-1045: 5,000x magnification



(5)

Cirrus Pharmaceuticals, Inc. Strategic Product Development

Confidential

Dimensional analysis was performed on SEM pictures of micronized lev tartrate API and lev tartrate from MDI sprays. The SEM imaging was performed as described in the Nov. 2001 update.

For the MDI lot, one spray was applied to the sample slide from a distance of approximately 5 cm. This resulted in particles that were well dispersed and could be readily measured after imaging. The API samples were prepared by distributing the powder as sparsely as possible across the sample slide. Still, for most pictures, particles were packed so densely that they could not be readily discriminated and measured. Of the 13 API samples imaged, only two were conducive to measuring most of the particles within the picture.

Within each picture, every particle was measured for which the length and width could be visually discerned. Dimensions were measured manually using ImageJ software (ver 1.26t) from the National Institutes of Health, with the scale shown on each picture used to calibrate the software.

Results are sumarized below:

Lot	Description	Picture #	# Particles Meesured	Avg Length (µm)	Avg Width (µm)	Avg L / W
041-0001	Micronized API	1	178	3.294	0.384	8.893
041-0005	Micronized API	2	100	3.661	0.449	8.646
011-002-06-136 Can # 8	Lead Formulation (prepared from 041-0001)	3	225	3.785	0.502	7.603
		4	233	3.381	0.448	7.609

The two API lots showed similar aspect ratios (8.9 and 8.6). The aspect ratio (7.6) for MDI lot 011-002-06-136 was slightly smaller compared to the aspect ratio (8.9) for the API lot from which it was prepared. MDI batch 011-002-06-136 was prepared on 5/29/01 from API batch 041-0001.

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Tel.: (919) 884-2064, Fax: (919) 884-2075, Web: www.CirrusPharm.com